	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	85	(DNA adj methylation) same inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:41			0
2	BRS	L2	202	(histone adj deacetylase) same inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:43			0
3	BRS	L3	165	(histone adj deacetylase) near inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:43			0
4	BRS	L5	39	(DNA adj methylation) near inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:45			0
5	BRS	L6	5585	(hydroxamic adj acid) or trichostatin or oxamflatin or (bishydroxamic adj acid) or pyroxamide	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:45			0
6	BRS	L7	3043	(cyclic adj peptide) or (trapoxin adj A) or apicidin or fr901228	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:46			0
7	BRS	L8	553	depsipeptide	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:47			0
8	BRS	L9	56970	butyrate or (butyric adj acid) or phenylburyrate or (arginine adj butyrate)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:47			0
9	BRS	L10	9	depudecin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:47			0
10	BRS	L11	11506	benzamide or MS-27-275	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:48			0
11	BRS	L12	200480	cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:49			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
12	BRS	L13	111415	(cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:49			0
13	BRS	L14	2	((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same ((histone adj deacetylase) near inhibitor) same ((DNA adj methylation) near inhibitor)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:50			0
14	BRS	L15	1	((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same (cytidine or decitabine) same (((hydroxamic adj acid) or trichostatin or oxamflatin or (bishydroxamic adj acid) or pyroxamide) or ((cyclic adj peptide) or (trapoxin adj A) or apicidin or fr901228) or depsipeptide or (butyrate or (butyric adj acid) or phenylburyrate or (arginine adj butyrate)) or depudecin)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:51			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
15	BRS	L16	142	((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same (cytidine or decitabine)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:52			0
16	BRS	L17	20	((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same (cytidine or decitabine) same (patient or subject)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:53			0
17	BRS	L18	19	((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same ((DNA adj methylation) near inhibitor)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:53			0
18	BRS	L19	15	((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same ((DNA adj methylation) near inhibitor) same (patient or subject)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:55			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
19	BRS	L20	32	(((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same (cytidine or decitabine) same (patient or subject)) or (((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same ((DNA adj methylation) near inhibitor) same (patient or subject))	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:55			0
20	BRS	L21	4	((((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same (cytidine or decitabine) same (patient or subject)) or (((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same ((DNA adj methylation) near inhibitor) same (patient or subject))) same dose	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:57			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
21	BRS	L22	0	((((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same (cytidine or decitabine) same (patient or subject)) or (((cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarcinoma or malignant or lymphoma or leukemia or melanoma) same treat$4) same ((DNA adj methylation) near inhibitor) same (patient or subject))) same (mg/m2)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:57			0
22	BRS	L23	1495	anti-neoplastic adj agent	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 08:59			0
23	BRS	L24	15720	(antibiotic adj agent) or doxorubicin or daunorubicin or epirubicin or idarubicin or anthracenedione or (mitomycin adj c) or bleomycin or dactinomycin or plicatomycin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 09:01			0
24	BRS	L25	16608	23 or 24	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 09:01			0
25	BRS	L26	1	21 same 25	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 09:03			0
26	BRS	L28	3	dimartino adj jorge.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/05/30 09:05			0

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FILE 'CAPLUS' ENTERED AT 10:55:54 ON 30 MAY 2003
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FILE 'SCISEARCH' ENTERED AT 10:55:54 ON 30 MAY 2003
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FILE 'AGRICOLA' ENTERED AT 10:55:54 ON 30 MAY 2003

=> s dna methylaion (p) inhibitor
L1             0 DNA METHYLAION (P) INHIBITOR

=> s (dna methylation) (p) inhibitor
L2          1383 (DNA METHYLATION) (P) INHIBITOR

=> s (histone deacetylase) (p) inhibitor
L3          3186 (HISTONE DEACETYLASE) (P) INHIBITOR

=> s (hydroxamic acid) or trichostatin or oxamflatin or (bishydroxamic acid) or pyroxamide
L4         12137 (HYDROXAMIC ACID) OR TRICHOSTATIN OR OXAMFLATIN OR (BISHYDROXAMI
                 C ACID) OR PYROXAMIDE

=> s (cyclic peptide) o (trapoxin A) or apicidin or fr901228
MISSING OPERATOR PEPTIDE) O
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s (cyclic peptide) or (trapoxin A) or apicidin or fr901228
L5          7512 (CYCLIC PEPTIDE) OR (TRAPOXIN A) OR APICIDIN OR FR901228

=> s depsipeptide
L6          3124 DEPSIPEPTIDE

=> s (butyrate or (butyric acid) or (phenylbutyrate) or (arginine butyrate)
UNMATCHED LEFT PARENTHESIS '(BUTYRATE'
The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s (butyrate) or (butyric acid) or (phenylbutyrate) or (arginine butyrate)
L7        110759 (BUTYRATE) OR (BUTYRIC ACID) OR (PHENYLBUTYRATE) OR (ARGININE
                 BUTYRATE)

=> s depudecin
L8             85 DEPUDECIN

=> s benzamide or ms-27-275
L9          25325 BENZAMIDE OR MS-27-275

=> s cytidine or decitabine
L10         33194 CYTIDINE OR DECITABINE

=> d his

     (FILE 'HOME' ENTERED AT 10:55:23 ON 30 MAY 2003)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     10:55:54 ON 30 MAY 2003
L1             0 S DNA METHYLAION (P) INHIBITOR
L2          1383 S (DNA METHYLATION) (P) INHIBITOR
L3          3186 S (HISTONE DEACETYLASE) (P) INHIBITOR
L4         12137 S (HYDROXAMIC ACID) OR TRICHOSTATIN OR OXAMFLATIN OR (BISHYDROX
L5          7512 S (CYCLIC PEPTIDE) OR (TRAPOXIN A) OR APICIDIN OR FR901228
L6          3124 S DEPSIPEPTIDE
L7        110759 S (BUTYRATE) OR (BUTYRIC ACID) OR (PHENYLBUTYRATE) OR (ARGININE
L8             85 S DEPUDECIN
L9          25325 S BENZAMIDE OR MS-27-275
L10         33194 S CYTIDINE OR DECITABINE
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=> s l2 or l10
L11      34494 L2 OR L10

=> s l3 or l4 or l5 or l6 or l7 or l8 or l9
L12     157445 L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9

=> s cancer or antineoplastic or carcinoma or scarcoma or myeloma or tumor or adenoma or adenocarc
   4 FILES SEARCHED...
L13    5347273 CANCER OR ANTINEOPLASTIC OR CARCINOMA OR SCARCOMA OR MYELOMA OR
               TUMOR OR ADENOMA OR ADENOCARCINOMA OR MALIGNANT OR LYMPHOMA OR
               LEUKEMIA OR MELANOMA

=> s l13 (p) treat? (p) patient
L14     180003 L13 (P) TREAT? (P) PATIENT

=> s l11 (p) l12 (p) l14
L15           2 L11 (P) L12 (P) L14

=> duplicat remove l15
DUPLICATE PREFERENCE IS 'CAPLUS, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L15
L16           2 DUPLICATE REMOVE L15 (0 DUPLICATES REMOVED)

=> d l16 1-2 ibib abs

L16  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:832643  CAPLUS
DOCUMENT NUMBER:          137:304765
TITLE:                    Compositions and methods for reestablishing gene
                          transcription through inhibition of DNA methylation
                          and histone deacetylase
INVENTOR(S):              Dimartino, Jorge
PATENT ASSIGNEE(S):       Supergen, Inc., USA
SOURCE:                   PCT Int. Appl., 54 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 2002085400      A1   20021031       WO 2002-US12092  20020419
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
             TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 2001-841744   A1 20010424
AB   Compns. and methods are provided for   ***treating***   diseases assocd.
     with aberrant silencing of gene expression such as   ***cancer***   by
     reestablishing the gene expression through inhibition of DNA
     hypomethylation and   ***histone***     ***deacetylase***   . The method
     comprises: administering to a   ***patient***   suffering from the disease
     a therapeutically effective amt. of a   ***DNA***     ***methylation***
       ***inhibitor***   such as a cysteine analog such as   ***decitabine***   ,
     in combination with an effective amt. of   ***histone***
       ***deacetylase***     ***inhibitor***   such as   ***hydroxamic***
       ***acid***   ,   ***cyclic***     ***peptide***   ,   ***benzamide***   ,
       ***butyrate***   , and   ***depudecin***   .
REFERENCE COUNT:          5     THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16  ANSWER 2 OF 2  BIOSIS  COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:   2002:261622  BIOSIS
DOCUMENT NUMBER:    PREV200200261622
TITLE:              Preclinical evaluation of the efficacy of STI571 in
                    combination with a variety of novel anticancer agents.
AUTHOR(S):          La Rosee, Paul (1); Johnson, Kara (1); Moseson, Erika M.
                    (1); O'Dwyer, Michael (1); Druker, Brian J. (1)
CORPORATE SOURCE:   (1) Division Hematology and Medical Oncol
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and Science University, Portland, OR USA
SOURCE: Blood, (Nov[redacted]er 16, 2001) Vol. 98, No. 11 P[redacted] 1, pp. 839a. http://www.bloodjournal.org/. print.
Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

AB STI571, a Bcr-Abl tyrosine kinase ***inhibitor*** has significant clinical activity in all phases of CML. Although durable responses have been seen in chronic phase patients, not all chronic phase patients achieve a cytogenetic response. Further, resistance or relapse during ***treatment*** with single agent STI571 have been observed in the majority of blast crisis patients. To determine whether the activity of STI571 could be enhanced, combinations of STI571 with other anti-leukemic agents were evaluated for activity against Bcr-Abl positive cell lines and in colony forming assays in vitro. We evaluated the cytotoxicity of arsenic trioxide (As2O3, Trisenox) and the chromatin modifiers 5-Aza-2-deoxycytidine (***decitabine***) and ***Trichostatin*** -A alone and in combination with STI571 against Bcr-Abl positive and negative cell lines and primary CML cells derived from chronic phase patients prior to ***treatment*** with STI571. As with other chemotherapeutic agents, significantly higher concentrations of As2O3 were required to achieve a 50% growth inhibition (IC50) of Bcr-Abl positive cell lines, K562 (1.11 muM+-0.075) and MO7p210 (1.99 muM+-0.22) than those required to inhibit the growth of Bcr-Abl negative cells, MO7e (0.81 muM+-0.18) and 32D (0.52 muM+-0.18). These levels of As2O3 are within a clinically achievable range. Cotreatment of K562 and MO7p210 cells with approximately equipotent doses of As2O3 and STI571 additively inhibits proliferation in a growth inhibition range up to 80%. Data analysis by the median-effect method (Chou & Talalay), which calculates the combination-index (CI) at different levels of inhibition, suggests that at >80% levels of inhibition, moderate synergy might be achievable. In colony forming assays using CML ***patient*** samples, combination ***treatment*** showed increased antiproliferative effects as compared with STI571 alone. Combinations of 0.1 or 0.25 muM STI571 with 0.4 or 0.8muM As2O3 (CFU-GM) and 0.8muM As2O3 (BFU-E) were significantly more potent in inhibiting colony formation as compared to ***treatment*** with STI571 alone. ***Decitabine*** is a hypomethylating agent that has activity in the ***treatment*** of CML blast crisis but has a narrow therapeutic window due to hematological toxicity. In MTT-assays with K562 cells, the combination of ***decitabine*** with STI571 revealed synergistic activity as seen by CI-values <1 at the IC50 (CI=0.6+-0.24) and IC75 (CI=0.6+-0.08) doses. This synergistic potential was also seen in MO7p210 cells (IC50: CI=0.81+-0.07 and IC75: CI=0.69+-0.1). Colony forming assays assessing the effects of ***decitabine*** on primary CML cells are ongoing. The triple combination of ***Trichostatin*** -A, a ***histone*** ***deacetylase*** ***inhibitor*** , ***decitabine*** and STI571 indicate antagonism (CI>1), which is in contrast to findings in non-leukemic ***malignant*** cell lines, where the combination of ***Trichostatin*** -A and ***decitabine*** led to enhanced apoptosis compared to single agent ***treatment*** . Experiments are ongoing with combination of ***Trichostatin*** -A and STI571 and ***Trichostatin*** -A with ***decitabine*** to determine which of these combinations accounts for this antagonism. These data suggest that combinations of STI571 with As2O3 or ***decitabine*** might be considered as therapeutic alternatives that could circumvent resistance to STI571, particularly in patients with advanced disease.

=> d his

(FILE 'HOME' ENTERED AT 10:55:23 ON 30 MAY 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 10:55:54 ON 30 MAY 2003

L1	0	S DNA METHYLAION (P) INHIBITOR
L2	1383	S (DNA METHYLATION) (P) INHIBITOR
L3	3186	S (HISTONE DEACETYLASE) (P) INHIBITOR
L4	12137	S (HYDROXAMIC ACID) OR TRICHOSTATIN OR OXAMFLATIN OR (BISHYDROX
L5	7512	S (CYCLIC PEPTIDE) OR (TRAPOXIN A) OR APICIDIN OR FR901228
L6	3124	S DEPSIPEPTIDE
L7	110759	S (BUTYRATE) OR (BUTYRIC ACID) OR (PHENYLBUTYRATE) OR (ARGININE
L8	85	S DEPUDECIN
L9	25325	S BENZAMIDE OR MS-27-275
L10	33194	S CYTIDINE OR DECITABINE

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L11       34494 S L2 OR L10
L12      157445 S L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9
L13     5347273 S CANCER OR ANTINEOPLASTIC OR CARCINOMA OR SCARCOMA OR MYELOMA
L14      180003 S L13 (P) TREAT? (P) PATIENT
L15           2 S L11 (P) L12 (P) L14
L16           2 DUPLICATE REMOVE L15 (0 DUPLICATES REMOVED)

=> s anti-neoplastic agent
L17         681 ANTI-NEOPLASTIC AGENT

=> s antiobiotic agent
L18           1 ANTIOBIOTIC AGENT

=> s doxorubicin or daunorubicin or epirubicin or idarubicin or anthracenedione or (mitomycin c) o
L19      287346 DOXORUBICIN OR DAUNORUBICIN OR EPIRUBICIN OR IDARUBICIN OR ANTHR
                ACENEDIONE OR (MITOMYCIN C) OR BLEOMYCIN OR DACTINOMYCIN OR
                PLICATOMYCIN

=> s l17 or l18 or l19
L20      287938 L17 OR L18 OR L19

=> s l16 (p) l20
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L135 (P) L128'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L141 (P) L131'
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FIELD CODE - 'AND' OPERATOR ASSUMED 'L143 (P) L132'
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FIELD CODE - 'AND' OPERATOR ASSUMED 'L145 (P) L133'
L21           0 L16 (P) L20

=> s l11 (p) l14
L22          88 L11 (P) L14

=> s l22 (p) dose
L23          51 L22 (P) DOSE

=> s l22 (p) (mg/m2)
'M2' IS NOT A VALID FIELD CODE
'M2' IS NOT A VALID FIELD CODE
'M2' IS NOT A VALID FIELD CODE
'M2' IS NOT A VALID FIELD CODE
'M2' IS NOT A VALID FIELD CODE
'M2' IS NOT A VALID FIELD CODE
L24           0 L22 (P) (MG/M2)

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KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L23
L25          15 DUPLICATE REMOVE L23 (36 DUPLICATES REMOVED)

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L25  ANSWER 1 OF 15     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   2003086733     IN-PROCESS
DOCUMENT NUMBER:    22486309   PubMed ID: 12599231
TITLE:              Long-term follow-up of a phase I study of high-dose
                    decitabine, busulfan, and cyclophosphamide plus allogeneic
                    transplantation for the treatment of patients with
                    leukemias.
AUTHOR:             De Lima Marcos; Ravandi Farhad; Shahjahan Munir; Andersson
                    Borje; Couriel Daniel; Donato Michele; Khouri Issa;
                    Gajewski James; Van Besien Koen; Champlin Richard; Giralt
                    Sergio; Kantarjian Hagop
CORPORATE SOURCE:   Department of Blood and Marrow Transplantation, The
                    University of Texas M. D. Anderson Cancer Center, Houston,
                    Texas.
SOURCE:             CANCER, (2003 Mar 1) 97 (5) 1242-7.
                    Journal code: 0374236. ISSN: 0008-543X.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals;
                    Priority Journals
ENTRY DATE:         Entered STN: 20030225
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Last Updated on STN: 20030225

AB BACKGROUND: ***Decitabine*** is a hypomethylating agent that has activity in patients with ***leukemia*** . The authors combined ***decitabine*** with busulfan and cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic stem cell transplantation. METHODS: Patients with high-risk acute myeloid ***leukemia*** (AML) (n = 12 patients); chronic myelomonocytic ***leukemia*** (CMML) (n = 1 ***patient***); acute lymphocytic ***leukemia*** (ALL) (n = 1 ***patient***); or late chronic phase, accelerated, or blastic phase chronic myelogenous ***leukemia*** (n = 9 patients) were eligible for the study. The ***treatment*** plan was comprised of busulfan, 12 mg/kg orally; cyclophosphamide, 100 mg/kg (n = 4 patients) or 120 mg/kg (n = 19 patients); and ***decitabine*** , intravenously at 3 ***dose*** levels: 400 mg/m(2) (n = 10 patients), 600 mg/m(2) (n = 8 patients), and 800 mg/m(2) (n = 5 patients). Donors were human leukocyte antigen-identical siblings in all cases, and all but one ***patient*** received peripheral blood stem cells. Graft-versus-host disease (GVHD) prophylaxis was tacrolimus based in all but one ***patient*** . RESULTS: The median time to neutrophil and platelet engraftment was 12.5 days and 17.5 days, respectively. Twenty-one patients were engrafted and achieved disease remission. At a median of 3.3 years posttransplantation, 26% of patients (40% of patients with AML) were alive and disease free. The median survival for the group was 17.2 months, and the disease free survival for the group was 8.9 months. Causes of death were disease recurrence (nine patients), chronic GVHD (four patients), infections (three patients), and acute GVHD (one ***patient***). The 100-day mortality rate was 9%. No ***decitabine*** ***dose*** -limiting toxicity was documented. The ***treatment*** -related mortality rate at 3 years was 35%. Responders were ***treated*** at all three ***decitabine*** ***dose*** levels, and no ***dose*** -response correlation was observed. CONCLUSIONS: There was a high response rate with low ***treatment*** -related mortality, with 26% of patients alive in remission 3.3 years after transplantation. ***Cancer*** 2003;97:1242-7.

DOI 10.1002/cncr.11184

L25 ANSWER 2 OF 15 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 2002470614 MEDLINE
DOCUMENT NUMBER: 22217424 PubMed ID: 12231523
TITLE: Phase I clinical trials of tezacitabine [(E)-2'-deoxy-2'-(fluoromethylene)cytidine] in patients with refractory solid tumors.
AUTHOR: Rodriguez Gladys I; Jones Richard E; Orenberg Elaine K; Stoltz Maxine L; Brooks Donald J
CORPORATE SOURCE: Cancer Therapy and Research Center, San Antonio, Texas 78207, USA.. grodrigu@saci.org
SOURCE: CLINICAL CANCER RESEARCH, (2002 Sep) 8 (9) 2828-34. Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20020917
Last Updated on STN: 20021213
Entered Medline: 20021104

AB PURPOSE: To evaluate safety, tolerability, and pharmacokinetics of a new nucleoside analogue, tezacitabine [(E)-2'-deoxy-2'-(fluoromethylene) ***cytidine*** (FMdC)] in patients with refractory solid tumors. EXPERIMENTAL DESIGN: Seventy patients were enrolled in four separate Phase I trials. Patients had metastatic or relapsed ***cancer*** of the colon, breast, pancreas, gastrointestinal tract, lung, and other sites. FMdC was administered by i.v. infusion over 30 min in one of four ***dose*** schedules--from once every 3 weeks to twice a week for 3 weeks, with ***dose*** escalation in each. Maximum doses ranged from 630 to 16 mg/m(2). RESULTS: Myelotoxicity, especially neutropenia, was the dominant toxicity and was generally ***dose*** -related. Grade 3 or 4 neutropenia occurred in 53% of patients but was of relatively short duration (1-8 days) in all of the patients. One ***patient*** experienced grade 3 thrombocytopenia and one ***patient*** grade 4 (duration 15 and 11 days, respectively). Transient febrile episodes were reported in 82% of patients with drug administration but were easily controlled. Drug-related gastrointestinal events were mild and appeared unrelated to ***dose*** . Pharmacokinetics were linear with ***dose*** not appreciably affected by

after single or multiple doses. Terminal half-life was 3-4 h and 23% of the administered drug was recovered in the urine as unchanged drug. The uridine analogue (FMdU), the deaminated metabolite of FMdC, was the primary metabolite. Objective antitumor activity was observed in eight patients: one exhibited a partial response and seven exhibited stable disease. CONCLUSIONS: In general, FMdC was well tolerated. On the basis of the time to recovery from neutropenia, the recommended schedule for Phase II studies is one ***treatment*** every 2 weeks, at a minimum ***dose*** of 270 mg/m(2).

L25 ANSWER 3 OF 15 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2002733704 IN-PROCESS
DOCUMENT NUMBER: 22384088 PubMed ID: 12495903
TITLE: Evidence- and consensus-based practice guidelines for the therapy of primary myelodysplastic syndromes. A statement from the Italian Society of Hematology.
AUTHOR: Alessandrino Emilio Paolo; Amadori Sergio; Barosi Giovanni; Cazzola Mario; Grossi Alberto; Liberato Lucio N; Locatelli Franco; Marchetti Monia; Morra Enrica; Rebulla Paolo; Visani Giuseppe; Tura Sante
CORPORATE SOURCE: Divisione di Ematologia, IRCCS Policlinico S. Matteo, Pavia; Italy.
SOURCE: HAEMATOLOGICA, (2002 Dec) 87 (12) 1286-306.
Journal code: 0417435. ISSN: 0390-6078.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20021227
Last Updated on STN: 20021227

AB BACKGROUND AND OBJECTIVES. Novel therapeutic agents and strategies have been introduced into the management of myelodysplastic syndromes (MDS) in the last years. This has led to more ***treatment*** options and a better chance of long-term survival for MDS patients, but also to uncertainty regarding the optimal use and possible side effects of these ***treatments*** . The Italian Society of Hematology commissioned a project to develop guidelines for the therapy of MDS using evidence-based knowledge and consensus-formation techniques. DESIGN AND METHODS. An Advisory Council (AC) shaped the project around a series of key clinical questions, performed a systematic search for evidence and graded the available evidence according to the Scottish Intercollegiate Guidelines Network (SIGN). A list of clinical questions was mailed to each of 10 senior hematologists composing the Expert Panel (EP): the panelists were asked to rank the most relevant questions, and to formulate answers to the questions according to the tables of evidence. A scenario phase followed, so as to reach a consensus on the three top ranked questions. The EP was asked to score ***patient*** profiles as appropriate or not appropriate for the therapeutic strategy under scrutiny, according to the RAND technique. Finally, from September 2001 to January 2002, four Consensus Conferences conducted according to the Nominal Group Technique were held in Milan, Italy. The overall goal of the conferences was to take a final decision upon the appropriateness of the uncertain scenarios and of the uncertain responses to the clinical questions. RESULTS. Evidence was judged sufficient for providing recommendations on the use of allogeneic stem cell transplantation, ***leukemia*** -like chemotherapy, autologous stem cell transplantation, low- ***dose*** chemotherapy, danazol, immunosuppressive therapy, hypomethylating agents and hematopoietic growth factors. Specific recommendations for supportive therapy, including iron chelation, were issued. Allogeneic stem cell transplantation was unanimously considered as the only curative ***treatment*** for MDS patients, and recommendations on its use were agreed based on ***patient*** 's age, risk, clinical features and donor availability. AML-like chemotherapy was also considered a valuable therapeutic option for subsets of MDS patients. Autologous stem cell transplantation was recommended for patients who lack an HLA identical donor and have achieved complete remission with AML-like chemotherapy. ***Decitabine*** , recombinant human erythropoietin and immunosuppressive therapy were judged valuable therapeutic options for subsets of MDS patients whereas low- ***dose*** cytarabine was not.Specific therapeutic strategies for those subjects younger than 18 years or older than 75 years and the strategy of watchful waiting were decided by ***patient*** -oriented questions. INTERPRETATION AND CONCLUSIONS. Using evidence and consensus, recommendations for the ***treatment*** of MDS were issued. Statements were graded according to the strength of the supporting evidence and uncertainty was explicitly declared.

L25 ANSWER 4 OF 15 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 2001644763 MEDLINE
DOCUMENT NUMBER: 21553700 PubMed ID: 11697326
TITLE: Five-chlorodeoxycytidine, a tumor-selective enzyme-driven radiosensitizer, effectively controls five advanced human tumors in nude mice.
AUTHOR: Greer S; Alvarez M; Mas M; Wozniak C; Arnold D; Knapinska A; Norris C; Burk R; Aller A; Dauphinee M
CORPORATE SOURCE: Department of Microbiology and Immunology, University of Miami School of Medicine, FL 33101, USA.
CONTRACT NUMBER: 1R41CA79272-01A (NCI)
SOURCE: INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, (2001 Nov 1) 51 (3) 791-806.
Journal code: 7603616. ISSN: 0360-3016.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011108
Last Updated on STN: 20020123
Entered Medline: 20011204

AB PURPOSE: The study's goals were as follows: (1) to extend our past findings with rodent tumors to human tumors in nude mice, (2) to determine if the drug protocol could be simplified so that only CldC and one modulator, tetrahydrouridine (H4U), would be sufficient to obtain efficacy, (3) to determine the levels of deoxycytidine kinase and dCMP deaminase in human tumors, compared to adjacent normal tissue, and (4) to determine the effect of CldC on normal tissue radiation damage to the cervical spinal cord of nude mice. METHODS AND MATERIALS: The five human tumors used were as follows: prostate tumors, PC-3 and H-1579; glioblastoma, SF-295; breast ***tumor*** , GI-101; and lung ***tumor*** , H-165. The duration of ***treatment*** was 3-5 weeks, with drugs administered on Days 1-4 and radiation on Days 3-5 of each week. The biomodulators of CldC were N-(Phosphonacetyl)-L-aspartate (PALA), an inhibitor of aspartyl transcarbamoylase, 5-fluorodeoxycytidine (FdC), resulting in ***tumor*** -directed inhibition of thymidylate synthetase, and H4U, an inhibitor of ***cytidine*** deaminase. The total ***dose*** of focused irradiation of the tumors was usually 45 Gy in 12 fractions. RESULTS: Marked radiosensitization was obtained with CldC and the three modulators. The average days in ***tumor*** regrowth delay for X-ray compared to drugs plus X-ray, respectively, were: PC-3 prostate, 42-97; H-1579 prostate, 29-115; glioblastoma, 5-51; breast, 50-80; lung, 32-123. Comparative studies with PC-3 and H-1579 using CldC coadministered with H4U, showed that both PALA and FdC are dispensable, and the protocol can be simplified with equal and possibly heightened efficacy. For example, PC-3 with X-ray and (1) no drugs, (2) CldC plus the three modulators, (3) a high ***dose*** of CldC, and (4) escalating doses of CldC resulted in 0/10, 3/9, 5/10, and 6/9 cures, respectively. The ***tumor*** regrowth delay data followed a similar pattern. After ***treating*** mice only 11/2 weeks with CldC + H4U, 92% of the PC-3 ***tumor*** cells were found to possess CldU in their DNA. The great majority of head-and-neck tumors from ***patient*** material had markedly higher levels of dC kinase and dCMP deaminase than found in adjacent normal tissue. Physiologic and histologic studies showed that CldC + H4U combined with X-ray, focused on the cervical spinal cord, did not result in damage to that tissue. CONCLUSIONS: 5-CldC coadministered with only H4U is an effective radiosensitizer of human tumors. Ninety-two percent of PC-3 ***tumor*** cells have been shown to take up ClUra derived from CldC in their DNA after only 11/2 weeks and 2 weeks of bolus i.p. injections. Enzymatic alterations that make tumors successful have been exploited for a therapeutic advantage. The great electronegativity, coupled with the relatively small Van der Waal radius of the Cl atom, may result in CldC's possessing the dual advantageous properties of FdC on one hand and BrdU and IdU on the other hand. These advantages include autoenhancing the incorporation of CldUTP into DNA by not only overrunning but also inhibiting the formation of competing TTP pools in tumors. A clinical trial is about to begin, with head-and-neck tumors as a first target of CldC radiosensitization.

L25 ANSWER 5 OF 15 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 2001566406 MEDLINE
DOCUMENT NUMBER: 21525467 PubMed ID: 11669297
TITLE: Evolving treatment options of myelodysplastic syndromes.
AUTHOR: Verbeek W; Ganser A
CORPORATE SOURCE: Medizinische Hochschule Hannover, Zentrum Innere Medizin, Abteilung Hamatologie/Onkologie, Germany..

SOURCE: ANNALS OF HEMATOLOGY, (2001 Sep) 80 (9) 499-5[illegible]. Ref: 81
Journal code: [illegible]107334. ISSN: 0939-5555.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011024
Last Updated on STN: 20020122
Entered Medline: 20011204

AB Myelodysplastic syndromes (MDS) comprise a heterogenous group of myeloid stem cell disorders characterized by peripheral cytopenias and dysplasia of bone marrow progenitor cells. A clonal evolution can result in progressive bone marrow failure and transformation towards acute myelogenous ***leukemia*** . A ***patient*** 's prognosis as estimated by the International Prognostic Scoring System, age, and co-morbidities have to be considered for the selection of various ***treatment*** options. Although supportive care remains standard therapy for low-risk MDS, a number of ***treatment*** approaches that aim to improve cytopenia in transfusion-dependent patients are currently under investigation. Among others, immunosuppressive, anticytokine, and antiangiogenic therapy will be discussed. The demethylating agents 5-azacytidine and ***decitabine*** are promising for the ***treatment*** of elderly patients with high-risk MDS. An increase of the upper age limit for allogeneic stem cell transplantation, the only curative ***treatment*** option, by the development of ***dose*** -reduced conditioning regimens may have implications for the ***treatment*** of MDS patients in the future.

L25 ANSWER 6 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000091410 EMBASE
TITLE: DNA methylation inhibitors in the treatment of leukemias, myelodysplastic syndromes and hemoglobinopathies: Clinical results and possible mechanisms of action.
AUTHOR: Lubbert M.
CORPORATE SOURCE: M. Lubbert, Department of Medicine, Division of Hematology/Oncology, Univ. of Freiburg Medical Center, Hugstetter Str. 55, D-79106 Freiburg, Germany. luebbert@mmll.ukl.uni-freiburg.de
SOURCE: Current Topics in Microbiology and Immunology, (2000) 249/- (135-164).
Refs: 103
ISSN: 0070-217X CODEN: CTMIA3
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB From results of clinical studies performed over more than 20 years with both azacitidine and ***decitabine*** in acute leukemias and MDS, one can conclude that both have comparable activity in these diseases. Relapsed and refractory AML and previously untreated high-risk MDS patients have been the most extensively studied subgroups with respect to drug schedule and effectivity. In relapsed/refractory AML (and CML in blast crisis), schedules with total doses ranging between 500 mg/m2 and 1500 mg/m2 with either drug are as effective (or are superior to) high- ***dose*** Ara-C. Lower ***dose*** schedules in the ***treatment*** of AML have been explored only in a limited number of studies, with inconclusive results regarding the best schedule and effectivity. The pioneering studies of the Aviano group have demonstrated the effectivity of several low- ***dose*** schedules in high-risk MDS (which often precedes AML of the elderly, since these patients often present with a clinical or morphologically detectable myelodysplastic phase). The majority of these AML patients are not eligible for intensive induction-consolidation ***treatment*** , due to their age and co-morbidity. Therefore, it would be of great interest to systematically study lower ***dose*** , first-line schedules of ***decitabine*** or azacitidine in this ***patient*** group. Outpatient schedules using subcutaneous injection would of course be very useful in this regard. The initial, rapid blast lysis that is typically induced by Ara-C often does not occur with methylation inhibitors. Therefore, combinations with hydroxyurea or Ara-C would probably be necessary to control clinically relevant leukocytosis present at the start of ***treatment*** .

effective when given over a prolonged period of repeated courses, which might be considered in the design of such protocols. Once the best response is achieved, DNA methylation inhibitors, given at even lower doses, may also be useful agents in the maintenance of these responses. The randomized phase-III study performed by the CALGB (SILVERMAN et al. 1998) has implicated azacitidine as a drug to alter the natural course of high-risk MDS. The very encouraging results of phase-II studies with ***decitabine*** also strongly urge for proof of its effectivity in a controlled study. Since about 50% of high-risk MDS patients do not respond to demethylating agents, rational drug combinations should be another step in further improving these results. Given the known myelotoxicity of these drugs in a disease presenting with cytopenias, clinically effective combinations with compounds that have little or no myelotoxicity are highly desirable. These may include HGFs and/or differentiating agents, such as all-trans retinoic acid which, as a single agent, probably has little activity in MDS, but may be more effective in the presence of ***decitabine*** due to upregulation of its receptor (COTE and MOMPARLER 1997). Since most MDS patients eventually relapse following ***treatment*** with azacitidine or ***decitabine*** , a prolongation of remission may possibly be achieved with a lower ***dose*** schedule as maintenance therapy. Other future studies might define a possible role of even lower ***dose*** schedules (with less myelotoxicity) in low-risk MDS and in other disorders that are responsive to DNA methylation inhibitors. KOSHY et al. (1998) recently reported that ***decitabine*** , at starting doses of 1.5 mg/kg per course (divided into ten doses of 0.15 mg/kg administered over 14 days), augments HbF levels in sickle-cell anemia patients. Other recurrent effects seen at this very low ***dose*** were mild neutropenia and an increase in platelet count. The promising early results of this interesting study imply that this drug exerts its mechanism(s) even at a total ***dose*** that is .apprx.50% of that used in high-risk MDS (notwithstanding different time schedules of administration). Further studies are necessary to define this activity in sickle cell patients that are refractory to HU with respect to duration of ***treatment*** , development of resistance, and potential carcinogenicity. The ongoing studies by Giralt and coworkers on ***decitabine*** in the allogeneic transplantation setting show that it is feasible to use this drug in preparative regimens in ***leukemia*** and MDS patients. Since the relapse rate of AML and MDS patients in non-intensive preparative regimens is high, the use of this compound, which can upregulate MHC class-I molecules in residual ***malignant*** cells and, therefore, improve antileukemic effects of donor-lymphocyte infusion, should be further defined. The phase-I/II studies of azacitidine and ***decitabine*** performed in the 1970s and 1980s, respectively, in patients with solid tumors have yielded disappointing results overall. However, with the knowledge derived from studies of single-agent DNA-methylation inhibitors in MDS and AML regarding effective drug schedules, the very limited non-hematologic toxicity and the necessity to administer these drugs over a prolonged period to achieve a progressive removal of ***malignant*** cells, it would be of interest to re-evaluate the activity of these drugs in solid tumors. The rationale for revisiting this issue could possibly be strengthened by recent investigations from several laboratories demonstrating hypermethylation and transcriptional silencing of ***tumor*** -suppressor genes (p16/INK4A, p15/INK4B, Rb, VHL) in different types of solid tumors. Results obtained on decreased methylation of p15 in mononuclear bone marrow cells from MDS ***treated*** with ***decitabine*** suggest hypermethylated genes as appropriate targets of DNA methylation inhibitors even at non-intensive ***dose*** schedules. Given their short plasma half-life, repeated administration of ***decitabine*** or azacitidine with prolonged infusion duration in solid tumors with known hypermethylation of p16, e.g., bladder ***cancer*** of non-small-cell lung ***cancer*** , might result in antitumor activity that is superior to the disappointing results obtained with 1-h infusion schedules. The available data on the mechanism of action of these drugs strengthen the idea that it is different from that of agents that act primarily via their cytotoxic effects, such as low- ***dose*** Ara-C. In 1984, Momparler et al. described the effect of ***decitabine*** in ***leukemia*** as probably involving '... gene activation and induction of differentiation. One would not expect to observe an acute cell kill, but a disorganization of gene expression and a gradual decrease in cell number due to senescence.' In fact, most investigators ***treating*** patients with MDS with these drugs have observed remissions obtained in the absence of true bone marrow aplasia and late remissions occurring months after stopping administration of these drugs. Since hypermethylation and silencing of ***tumor*** -suppressor genes involved in cell-cycle regulation is frequent in ***leukemia*** and MDS, demethylation and reactivation of such genes might, at least in

phenomena. It is tempting to speculate what other groups of genes may be subject to demethylation in diseases that are responsive to DNA methylation inhibitors. Pinto has reported upregulation of granulocyte-colony-stimulating-factor receptor on bone marrow cells from a ***patient*** with MDS ***treated*** with ***decitabine*** (PINTO and ZAGONEL 1993), which would be an attractive, simple explanation for the observed improvement of granulocytopenia in responding patients. Similarly, improvement of anemia and rapid induction of thrombocytosis in this disease following ***treatment*** with DNA-methylation inhibitors could be speculated to be due to upregulation of lineage-specific receptor molecules. Clonality studies on granulocytes mobilized in responding MDS patients may clarify whether the activity of DNA methylation inhibitors is via differentiation induction. Finally, with further evidence that DNA demethylation induced by both drugs is linked to their clinical activities, combinations with other compounds inhibiting methylation but lacking myelotoxicity, such as antisense oligonucleotides inhibiting Dnmt1 (RAMCHANDANI et al. 1997), would be very interesting combinations in diseases where azacitidine and ***decitabine*** are active.

L25 ANSWER 7 OF 15 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 2000420723 MEDLINE
DOCUMENT NUMBER: 20288954 PubMed ID: 10830142
TITLE: A phase I trial of cisplatin plus decitabine, a new DNA-hypomethylating agent, in patients with advanced solid tumors and a follow-up early phase II evaluation in patients with inoperable non-small cell lung cancer.
AUTHOR: Schwartsmann G; Schunemann H; Gorini C N; Filho A F; Garbino C; Sabini G; Muse I; DiLeone L; Mans D R
CORPORATE SOURCE: South-American Office for Anticancer Drug Development, and Hospital de Clinicas de Porto Alegre (HCPA-UFRGS), RS, Brazil.
SOURCE: INVESTIGATIONAL NEW DRUGS, (2000 Feb) 18 (1) 83-91. Journal code: 8309330. ISSN: 0167-6997.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20000915
Last Updated on STN: 20000915
Entered Medline: 20000901

AB The authors describe a phase I trial of cisplatin plus ***decitabine*** , a novel DNA-hypomethylating agent, in patients with advanced solid tumors, which was followed by an early phase II evaluation of the combination in patients with inoperable non-small cell lung ***cancer*** (NSCLC). In the phase I trial, cisplatin was studied at a fixed ***dose*** of 33 mg/m2, while ***decitabine*** was escalated in four (I-IV) ***dose*** escalation levels (45, 67, 90 to 120 mg/m2, respectively) in consecutive groups of at least 3 patients per ***dose*** level. Decytabine was administered to the patients as a two-hour intravenous infusion, while cisplatin was given intravenously immediately after the end of ***decitabine*** infusion. Both agents were given on days 1-3 every 21 days. Twenty-one patients were included in the phase I trial. ***Dose*** level IV (120 mg/m2 ***decitabine***) was considered the maximum tolerated ***dose*** (MTD), while the ***dose*** -limiting toxicities were neutropenia, thrombocytopenia and mucositis. The recommended doses for phase II trials in good- and poor-risk patients were 90 (level III) and 67 mg/m2 (level II), respectively. One short-lasting partial response was observed in a ***patient*** with cervical ***cancer*** , while two minor regression were documented in a patients with NSCLC and cervical ***cancer*** , respectively. ***Dose*** level II was selected for the phase II trial in patients with inoperable NSCLC. Fourteen consecutive patients were included in this part of the study. The median age of the patients was 57 years (range, 39-75), male/female ratio of 11/3 and a median WHO performance status 1 (0-2). The stage of disease were IIIB (5) and IV (9). Prior irradiation to the chest was given in one case. A total of 30 ***treatment*** courses were evaluable for toxicity and response, with a median of 2 courses per ***patient*** (1-4). Grade 3-4 neutropenia and thrombocytopenia were observed in about half of the cases. Mucositis, diarrhea, nausea and vomiting, and skin rash were also observed in some patients. Three minor responses were documented, which lasted for 4, 16 and 36 weeks. Median survival of patients was 15 weeks (4-38). In

exhibit significant antitumour activity in patients with NSCLC at the ***dose*** and schedule applied in this trial to justify its further evaluation in this ***patient*** population.

L25 ANSWER 8 OF 15 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1999438572 MEDLINE
DOCUMENT NUMBER: 99438572 PubMed ID: 10509156
TITLE: Severe pulmonary toxicity in patients treated with a combination of docetaxel and gemcitabine for metastatic transitional cell carcinoma.
AUTHOR: Dunsford M L; Mead G M; Bateman A C; Cook T; Tung K
CORPORATE SOURCE: CRC Wessex Medical Oncology Unit, Department of Histopathology and Radiology, Southampton University Hospitals, UK.
SOURCE: ANNALS OF ONCOLOGY, (1999 Aug) 10 (8) 943-7.
Journal code: 9007735. ISSN: 0923-7534.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991116
AB BACKGROUND: Both gemcitabine and docetaxel have been associated with pulmonary toxicity when used as single agents. We report a study in which three of five cases developed pulmonary toxicity (which proved fatal in one case) when these drugs were used in combination to ***treat*** metastatic transitional cell ***cancer*** . PATIENTS AND METHODS: Three patients developed dyspnoea, in two cases associated with pulmonary infiltrates, whilst receiving the combination of gemcitabine and docetaxel in a phase I trial. The case notes of all five patients entered into this trial were studied. A literature review was undertaken to gain information on reported pulmonary toxicity with the deoxy- ***cytidine*** analogues and taxanes given alone or in combination with or without radiotherapy. RESULTS: Three patients developed delayed dyspnoea whilst receiving gemcitabine/docetaxel in combination. This settled with cessation of ***treatment*** in one ***patient*** , however in the remaining two cases significant hypoxia developed, associated radiologically with evidence of progressive pulmonary infiltrates. One of these patients developed respiratory failure after bronchoscopy and biopsy and died. His chest X-ray changes were consistent with adult respiratory distress syndrome. The transbronchial biopsy and post mortem lung histology in this ***patient*** showed diffuse alveolar damage. The remaining ***patient*** settled with high ***dose*** prednisolone but died subsequently of progressive metastatic disease. CONCLUSION: The combination of gemcitabine and docetaxel showed promising activity in this small study. The development of pulmonary symptoms in three cases with radiological lung infiltrates in two other cases was cause for concern. Patients receiving this drug combination should be closely monitored for similar problems.

L25 ANSWER 9 OF 15 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 2000095559 MEDLINE
DOCUMENT NUMBER: 20095559 PubMed ID: 10630095
TITLE: Discovery and development of novel anticancer drug capecitabine.
AUTHOR: Ishitsuka H; Shimma N; Horii I
CORPORATE SOURCE: Nippon Roche Research Center, Nippon Roche K. K., Kamakura, Japan.
SOURCE: YAKUGAKU ZASSHI. JOURNAL OF THE PHARMACEUTICAL SOCIETY OF JAPAN, (1999 Dec) 119 (12) 881-97. Ref: 49
Journal code: 0413613. ISSN: 0031-6903.
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Japanese
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000426
AB Capecitabine (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine) is a novel

converted to 5-fluorouracil (5-FU) by three enzymes located in the liver and in tumors. N4-alkoxycarbonyl-5'-deoxy-5-fluorocytidine derivatives including capecitabine pass intact through the intestinal tract and are sequentially converted to 5-FU by a cascade of the three enzymes. The first step is the conversion to 5'-deoxy-5-fluorocytidine (5'-DFCR) by carboxylesterase located in the liver, then to 5'-deoxy-5-fluorouridine (5'-DFUR) by ***cytidine*** deaminase highly expressed in the liver and various solid tumors, and finally to 5-FU by thymidine phosphorylase (dThdPase) preferentially located in ***tumor*** tissues. Among large numbers of the derivatives, capecitabine was selected based on its susceptibility to hepatic carboxylesterase, oral bioavailability in monkeys and efficacy in a human ***cancer*** xenograft. Capecitabine given orally yielded substantially higher concentrations of 5-FU within tumors than in plasma or normal tissue (muscle). The ***tumor*** 5-FU levels were also much higher than those achieved by intraperitoneal administration of 5-FU at equi-toxic doses. This ***tumor*** selective delivery of 5-FU ensured greater efficacy and a more favourable safety profile than with other fluoropyrimidines. In 24 human ***cancer*** xenograft models studied, capecitabine was more effective at a wider ***dose*** range and had a broader spectrum of antitumor activity than 5-FU, UFT or its intermediate metabolite 5'-DFUR. The susceptibility of the xenografts to capecitabine correlated with ***tumor*** dThdPase levels. Moreover, the conversion of 5'-DFUR to 5-FU by dThdPase in ***tumor*** was insufficient in a xenograft model refractory to capecitabine. In addition, the efficacy of capecitabine was enhanced by dThdPase up-regulators, such as by taxanes and cyclophosphamide and by X-ray irradiation. The efficacy of capecitabine may, therefore, be optimized by selecting the most appropriate ***patient*** population based on dThdPase status and/or by combining it with dThdPase up-regulators. Capecitabine has additional characteristics not found with 5-FU, such as potent antimetastatic and anticachectic actions in mouse ***tumor*** models. With these profiles, capecitabine may have substantial potential in ***cancer*** ***treatment*** .

L25 ANSWER 10 OF 15 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 2000021594 MEDLINE
DOCUMENT NUMBER: 20021594 PubMed ID: 10555123
TITLE: Leucovorin, 5-fluorouracil, and gemcitabine: a phase I study.
AUTHOR: Poplin E; Roberts J; Tombs M; Grant S; Rubin E
CORPORATE SOURCE: The Massey Cancer Center of the Medical College of Virginia, Virginia Commonwealth University, Richmond, USA.
SOURCE: INVESTIGATIONAL NEW DRUGS, (1999) 17 (1) 57-62.
Journal code: 8309330. ISSN: 0167-6997.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 20000114
Last Updated on STN: 20000114
Entered Medline: 20000104

AB Gemcitabine is a chemotherapy agent with efficacy in the ***treatment*** of lung, pancreas, bladder and breast ***cancer*** . It inhibits DNA synthesis by interfering with ***cytidine*** triphosphate production and also inhibits the activity of ribonucleotide reductase. Gemcitabine may potentiate fluorouracil's inhibition of thymidylate synthase. This inhibition would be expected to be sequence dependent, occurring only if gemcitabine were administered following fluorouracil (5FU). The combination of leucovorin, 5-FU, and gemcitabine was assessed in this phase I trial. Eligibility requirements included refractory solid ***tumor*** malignancy; adequate hematologic, renal and hepatic reserve; no prior therapy with the combination of leucovorin and 5FU, or with gemcitabine; ECOG performance status 0-2, and signed informed consent. Eleven men and nine women were eligible. The median age was 52.5 years and the median performance status was 1. All but three patients had prior chemotherapy. The starting doses were leucovorin 20 mg/m2, 5FU 255 mg/m2 and gemcitabine 600 mg/m2. 5FU and gemcitabine were escalated in tandem to 340 mg/m2 and 800 mg/m2 and thereafter to 425 mg/m2 and 1000 mg/m2, respectively. Gemcitabine administration always followed that of 5FU by 30 minutes. The median number of cycles was 2 (range 1-32). Two patients at the starting ***dose*** had disease progression within the first cycle with one death on day 28. One ***patient*** with

months. There were no other responses. The maximum tolerated ***dose*** is leucovorin 20 mg/m2, 5FU 340 mg/m2, and gemcitabine 800 mg/m2. The impact of drug sequence remains undetermined.

L25 ANSWER 11 OF 15 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:79798 CAPLUS
DOCUMENT NUMBER: 126:152479
TITLE: YNK01, an oral cytosine arabinoside derivative in acute myeloid leukemia and chronic myeloid leukemia
AUTHOR(S): Heussner, P.; Willemze, R.; Ganser, A.; Hanauske, A.; Amadori, S.; Heil, G.; Schleyer, E.; Hiddemann, W.; Selbach, J.; et al.
CORPORATE SOURCE: Department of Hematology and Oncology, University of Medicine, Rostock, Germany
SOURCE: Haematology and Blood Transfusion (1997), 38(Acute Leukemias VI), 882-885
CODEN: HBTRDV; ISSN: 0171-7111
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Twenty-eight patients with acute myeloid ***leukemia*** (AML) and chronic myeloid ***leukemia*** (CML) were ***treated*** in a phase I/II multicenter trial and pilot single-center trial with YNK01 an oral cytosine arabinoside (ara-C) deriv. In contrast to ara-C, YNK01 is resistant to ***cytidine*** deaminases. Therefore YNK01 is converted to ara-C in the liver and released slowly into blood. It has been shown in ongoing pharmacokinetic studies that a mean of 16% of YNK01 is secreted as ara-U into the urine. Twenty-two patients with AML (12 patients with relapse, five with secondary AML, five with primary, not qualifying for intensive chemotherapy) were included, median age 67 (range 22-79 yr, 13 pretreated /11 with ara-C). In the AML trial the doses of YNK01 were escalated interindividually from a daily 100 mg/kg body wt. up to 1200 mg/kg body wt. for 14 days. Cycles were repeated every 21-28 days. Major toxicities at the 900- and 1200-mg ***dose*** levels were nausea grade 3 (WHO) in one ***patient*** ; diarrhea grade 3 in five patients, grade 4 in one ***patient*** ; exanthema grade 3 in one ***patient*** ; and stomatitis grade 3 in one ***patient*** , grade 4 in one ***patient*** . At the lower ***dose*** levels no grade 3 or 4 organ toxicities were obsd. Six patients (median age 53 yr, range 26-64 yr) were included in the CML pilot trial. ***Treatment*** was started with interferon (IFN)-.alpha.-2b5 .times. 106 units s.c. daily. After 1 wk YNK01 600 mg daily continuously was added. IFN and YNK01 were modified according to toxicity and effectivity. Maximum toxicities were diarrhea grade 3 in one ***patient*** bone pain grade 3 in one ***patient*** . In AML patients complete remission (CR) was obsd. in two of 21 patients, partial remission (PR) in one of 21 patients, and stable disease for up to 70 mo in four of 21 patients. In CML six of six patients achieved a complete hematol. response (CHR) after 7 mo of continuous ***treatment*** and two of six patients had a partial cytogenetic response (PCR), and two of six patients are in minor cytogenetic response (MCR). We conclude that YNK01 has a mild toxicity profile in patients with hematol. malignancies. Diarrhea seems to become the ***dose*** -limiting toxicity. The max. tolerable ***dose*** of YNK01 seems to be reached at the 1200-mg ***dose*** level in AML. Phase II studies will be performed to further evaluate the efficacy of the drug in AML patients as a maintenance ***treatment*** and in CML following the pilot trial.

L25 ANSWER 12 OF 15 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 10
ACCESSION NUMBER: 1995:935567 CAPLUS
DOCUMENT NUMBER: 124:44962
TITLE: Phase I clinical trial of continuous infusion cyclopentenyl cytosine
AUTHOR(S): Politi, Pedro M.; Xie, Fuming; Dahut, William; Ford, Harry Jr.; Kelley, James A.; Bastian, Anne; Setser, Ann; Allegra, Carmen J.; Chen, Alice P.; et al.
CORPORATE SOURCE: Division Cancer Treatment, National Cancer Institute, Bethesda, MD, 20889, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1995), 36(6), 513-23
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclopentenyl cytosine (CPE-C) is an investigational drug that is active against human solid ***tumor*** xenografts. The 5'-triphosphate of

conducted a phase I clin. trial of CPE-C given as a 24-h continuous i.v. infusion every 3 wk in 26 patients with solid tumors. The starting ***dose*** rate, 1 mg/m2 per h, was selected on the basis of both preclin. studies and pharmacokinetic data from two patients obtained after a test ***dose*** of 24 mg/m2 CPE-C as an i.v. bolus. ***Dose*** escalation was guided by clin. toxicity. A total of 87 cycles were given, and ten patients received four or more cycles. The mean CPE-C steady-state plasma levels (Cpss) increased linearly from 0.4 .mu.M to 3.1 .mu.M at ***dose*** levels ranging from 1 to 5.9 mg/m2 per h (actual body wt.); the mean total body clearance was 146 .+-. 38 mL/min per m2. CPE-C was eliminated by both renal excretion of intact drug and deamination to cyclopentenyl uracil in an apparent 2:1 ratio. CTP synthase activity in intact bone marrow mononuclear cells was inhibited by 58% to 100% at 22 h compared to matched pretreatment samples at all CPE-C ***dose*** levels. When all data were combined, flux through CTP synthase was decreased by 89.6% .+-. 3.1% at 22 h (mean .+-. SE, n = 16), and remained inhibited by 67.6% .+-. 7.7% (n = 10) for at least 24 h post-CPE-C infusion. Granulocyte and platelet toxicities were ***dose*** -dependent, and ***dose*** -limiting myelosuppression occurred during the initial cycle in two of three patients ***treated*** with 5.9 mg/m2 per h. Four of 11 patients (4 of 20 cycles) who received 4.7 mg/m2 per h CPE-C experienced hypotension 24-48 h after completion of the CPE-C infusion during their first (n = 2), third (n = 1) and sixth cycles (n = 1), resp. Two of these patients died with refractory hypotension despite aggressive hydration and cardiopulmonary resuscitation. One of 12 patients (28 total cycles) ***treated*** with 3.5 mg/m2 per h CPE-C experienced orthostatic hypotension during cycle 1, and this ***patient*** had a second episode of orthostatic hypotension at a lower ***dose*** (3.0 mg/m2 per h). Hypotension was not seen in patients receiving .ltoreq. 2.5 mg/m2 per h CPE-C. The occurrence of hypotension did not directly correlate with either CPE-C Cpss, CPE-U plasma levels, pretreatment ***cytidine*** plasma levels, baseline CTP synthase activity, or with the degree of enzyme inhibition during ***treatment*** . While the hypotension appeared to be ***dose*** -related, its unpredictable occurrence and the uncertainty concerning the mechanism preclude a recommendation of a tolerable ***dose*** for future studies.

L25 ANSWER 13 OF 15 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 89248978 MEDLINE
DOCUMENT NUMBER: 89248978 PubMed ID: 2720661
TITLE: Development of resistance to 1-beta-D-arabinofuranosylcytosine after high-dose treatment in childhood lymphoblastic leukemia: analysis of resistance mechanism in established cell lines.
AUTHOR: Kees U R; Ford J; Dawson V M; Piall E; Aherne G W
CORPORATE SOURCE: Clinical Immunology Research Unit, Princess Margaret Hospital, Perth, Western Australia.
SOURCE: CANCER RESEARCH, (1989 Jun 1) 49 (11) 3015-9.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198906
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19970203
Entered Medline: 19890623

AB Cell lines PER-163 and PER-164 are derived from a ***patient*** with acute lymphoblastic ***leukemia*** who developed resistance to 1-beta-D-arabinofuranosylcytosine (ara-C) after high- ***dose*** (HD) therapy. Both lines are highly resistant to ara-C and have maintained stable resistance for more than 18 mo. The resistance in PER-164 cells is the result of a selection process in vivo only, while PER-163 cells have in addition been exposed to ara-C in culture. Comparison with cell line PER-145, which is sensitive to ara-C and was established from the same ***patient*** before HDara-C therapy, revealed no differences with respect to surface markers, morphology, cytochemical stains, or requirements for growth in vitro. The leukemic origin of the three cell lines is indicated by the close similarities of all three cell lines to the ***patient*** 's fresh cells. The analysis of the two resistant cell lines shows that resistance to ara-C is not due to lower ara-C transport capacity nor to cytokinetic reasons, since the percentage of cells in S-phase is similar in all three cell lines. In addition, the resistant cell lines do not show any increased ***cytidine*** deaminase activity. PER-164 cells show a markedly reduced deoxycytidine

an enzyme activity of 21.48 pmol/h/mg of protein. In PER-163 cells, no deoxycytidine kinase activity could be detected. Furthermore, the two resistant cell lines show significantly different dCTP levels. The sensitive PER-145 cells generated 97.9 pmol of 1-beta-D-arabinofuranosylcytosine triphosphate (ara-CTP)/10(7) cells during a 45-min incubation period in the presence of 10(-6) M ara-C. This contrasts with 0.16 and 12 pmol of ara-CTP/10(7) cells for PER-163 and PER-164 cells, respectively. These investigations suggest that cell phenotypes with distinct features can be generated after HDara-C ***treatment*** and that decreased deoxycytidine kinase activity appears to be one of the major mechanisms of resistance.

L25 ANSWER 14 OF 15 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 88327740 MEDLINE
DOCUMENT NUMBER: 88327740 PubMed ID: 3416311
TITLE: Phase I clinical trial of a combination of dipyridamole and acivicin based upon inhibition of nucleoside salvage.
AUTHOR: Willson J K; Fischer P H; Tutsch K; Alberti D; Simon K; Hamilton R D; Bruggink J; Koeller J M; Tormey D C; Earhart R H; +
CORPORATE SOURCE: University of Wisconsin Clinical Cancer Center, Madison 53792.
CONTRACT NUMBER: NCI-CM-47663-28 (NCI)
SOURCE: CANCER RESEARCH, (1988 Oct 1) 48 (19) 5585-90.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198810
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19881025

AB A Phase I clinical trial of simultaneous 72-h infusions of dipyridamole and acivicin was carried out in patients with advanced malignancies. The objective of this trial was to determine the maximum tolerated ***dose*** of dipyridamole when administered as a 72-h infusion in combination with acivicin. The development of this combination is of interest because of in vitro observations which demonstrate that dipyridamole potentiates the cytotoxic action of acivicin by blocking nucleoside salvage. Patients were ***treated*** with concomitant i.v. infusions of dipyridamole and acivicin for 72 h. The acivicin ***dose*** infused remained constant during the trial at 60 mg/m2/72 h. The maximum tolerated ***dose*** (MTD) of dipyridamole was 23.1 mg/kg/72 h. Limiting toxicities at the MTD of dipyridamole with acivicin were severe gastrointestinal and constitutional symptoms which appeared to be caused by the high doses of dipyridamole administered. Escalation of dipyridamole did not potentiate the mild myelosuppression or the neurotoxicity which occurs with acivicin alone. At a ***dose*** of dipyridamole which was well below the MTD, one ***patient*** experienced symptomatic orthostatic hypotension, and another ***patient*** with coronary artery disease developed dizziness and transient electrocardiogram abnormalities. However, no other hypotensive or cardiovascular events occurred as dipyridamole was escalated to the MTD. Phlebitis occurred at the site of infusion when the ***dose*** of dipyridamole exceeded 13.5 mg/kg/72 h. Because of this local toxicity, it was necessary to administer dipyridamole through a central venous catheter to achieve maximum plasma levels. At the MTD of dipyridamole, steady-state total and free plasma levels of 11.9 microM and 27.8 nM, respectively, were attained by 24 h. These are free dipyridamole levels which in vitro were sufficient to block ***cytidine*** salvage and to potentiate the biochemical and cytotoxic effects of acivicin against human colon ***cancer*** cells (P.H. Fischer et al., ***Cancer*** Res., 44:3355-3359, 1984).

L25 ANSWER 15 OF 15 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 13
ACCESSION NUMBER: 1978:183118 CAPLUS
DOCUMENT NUMBER: 88:183118
TITLE: Clinical, biological, and biochemical effects of Pyrazofurin
AUTHOR(S): Cadman, Edwin C.; Dix, Douglas E.; Handschumacher, Robert E.
CORPORATE SOURCE: Dep. Pharmacol., Yale Univ. Sch. Med., New Haven, CT, USA
SOURCE: Cancer Research (1978), 38(3), 682-8
CODEN: CNREA8; ISSN: 0008-5472
DOCUMENT TYPE: Journal

LANGUAGE: English
GI

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AB Extensive conversion of Pyrazofurin (I) [30868-30-5] to the I 5'-PO4 [65446-02-8] and higher phosphorylated derivs. occurred in naturally sensitive (Walker 256 carcinosarcoma) and resistant (L5178Y ***leukemia***) tumors. A similar degree of conversion to phosphorylated derivs. was seen in acute myelogenous leukemic cells from patients. The insensitivity of the L5178Y ***leukemia*** may result from its greater capacity to utilize uridine [58-96-8] in the presence of I. Furthermore, L5178Y cells in culture can survive uridine deprivation for much longer periods than can the Walker 256 ***tumor*** . Although intracellular concns. of both uridine triphosphate [63-39-8] and ***cytidine*** triphosphate [65-47-4] are depleted in culture, only a transient decrease is seen in the concn. of ***cytidine*** triphosphate in L5178Y ascites cells from mice. The redns. in pyrimidine nucleotide pools may be responsible for the synergistic growth-inhibitory effects obsd. when I is combined with 5-fluorodeoxyuridine [50-91-9] or 1-.beta.-D-arabinofuranosylcytosine [147-94-4]. In patients, blockade of the metab. of carboxyl-14C-labeled orotate [65-86-1] was greater than 99% 15 min and 24 h after a single i.v. ***dose*** of I (200 mg/m2). In 17 patients given weekly i.v. therapy, no complete remissions or major regressions of ***tumor*** masses were seen. Antitumor effect was obsd. in 2 of 3 patients with acute myelogenous ***leukemia*** and in 1 ***patient*** each with erythroleukemia, mycosis fungoides, and psoriasis. The limiting toxicity was oral mucositis; depression or erythropoiesis was apparent in all patients ***treated*** for more than 4 wk.

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(FILE 'HOME' ENTERED AT 10:55:23 ON 30 MAY 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 10:55:54 ON 30 MAY 2003

L1	0	S	DNA METHYLAION (P) INHIBITOR
L2	1383	S	(DNA METHYLATION) (P) INHIBITOR
L3	3186	S	(HISTONE DEACETYLASE) (P) INHIBITOR
L4	12137	S	(HYDROXAMIC ACID) OR TRICHOSTATIN OR OXAMFLATIN OR (BISHYDROX
L5	7512	S	(CYCLIC PEPTIDE) OR (TRAPOXIN A) OR APICIDIN OR FR901228
L6	3124	S	DEPSIPEPTIDE
L7	110759	S	(BUTYRATE) OR (BUTYRIC ACID) OR (PHENYLBUTYRATE) OR (ARGININE
L8	85	S	DEPUDECIN
L9	25325	S	BENZAMIDE OR MS-27-275
L10	33194	S	CYTIDINE OR DECITABINE
L11	34494	S	L2 OR L10
L12	157445	S	L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9
L13	5347273	S	CANCER OR ANTINEOPLASTIC OR CARCINOMA OR SCARCOMA OR MYELOMA
L14	180003	S	L13 (P) TREAT? (P) PATIENT
L15	2	S	L11 (P) L12 (P) L14
L16	2		DUPLICATE REMOVE L15 (0 DUPLICATES REMOVED)
L17	681	S	ANTI-NEOPLASTIC AGENT
L18	1	S	ANTIOBIOTIC AGENT
L19	287346	S	DOXORUBICIN OR DAUNORUBICIN OR EPIRUBICIN OR IDARUBICIN OR AN
L20	287938	S	L17 OR L18 OR L19
L21	0	S	L16 (P) L20
L22	88	S	L11 (P) L14
L23	51	S	L22 (P) DOSE
L24	0	S	L22 (P) (MG/M2)
L25	15		DUPLICATE REMOVE L23 (36 DUPLICATES REMOVED)

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